Photo induced denaturation of tumour tissue inside the bladder in outpatient setting

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Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 August 2016 (11.08.2016)

WIPO | PCT

(10) International Publication Number
WO 2016/124745 A1

(51) International Patent Classification:
A61B 18/24 (2006.01) *A61N 5/06* (2006.01)
A61B 1/06 (2006.01) *A61B 1/307* (2006.01)

(21) International Application Number:
PCT/EP2016/052521

(22) International Filing Date:
5 February 2016 (05.02.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15153969.9 5 February 2015 (05.02.2015) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH,

[Continued on next page]

(54) Title: PHOTO INDUCED DENATURATION OF TUMOUR TISSUE INSIDE THE BLADDER IN OUTPATIENT SETTING

(57) Abstract: A system and a method for photo denaturation for in vivo treatment of tumour tissue inside the bladder is disclosed herein.

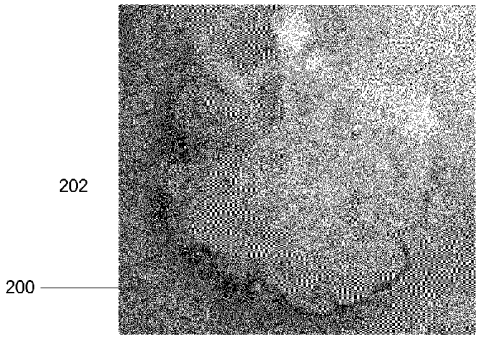


Fig. 2c

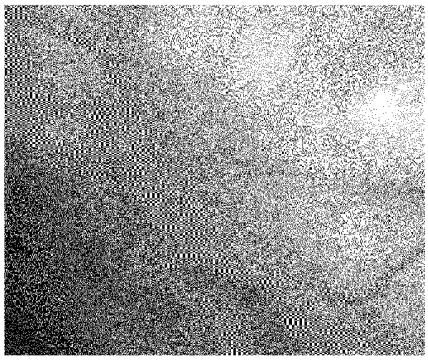


Fig. 2e

WO 2016/124745 A1

GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

Photo induced denaturation of tumour tissue inside the bladder in outpatient setting

The invention relates to the use of solid state light source photo induced denaturation for in vivo treatment of tumour tissue inside the bladder, where the solid state light source may be a high power LED (light emitting diode), a fibre laser, a diode laser or similar.

Background

Bladder tumour disease is a disease normally experienced by elderly people with a median age of bladder tumours debut at 65 years. Less straining treatment is required, as populations and thus also patients get older and suffer from more comorbidity making them less fit for admittance to hospital and general anaesthesia.

Urothelial cancer of the bladder is the second most expensive cancer disease and the one of the most common cancer types detected in Europe. About 75% of the patients suffer from non-muscle invasive bladder cancer (NMIBC) and account for approximately 65% of the cost of bladder cancer treatment.

NMIBC is normally removed in general anaesthesia either by admitting the patient for two-three days to a urology ward or in day-surgery settings. Generally, the prognosis of NMIBC is good, although 30–80% of cases will recur. In 1–45% of the cases NMIBC will progress to muscle invasion within 5 years. Consequently, NMIBC is a chronic disease with varying oncologic outcomes.

Traditionally, laser vaporization (LV) of bladder tumours to minimize surgical load or transurethral resection of bladder tumours (TUR-BT) has been tested for removing bladder tumours. Frequent recurrences requiring TUR-BT and lifelong surveillance account for the vast part of the treatment expenses, makes the cost per patient from diagnosis to death the highest of all cancer types.

Substantial health and patient resources can be spared if use of new technology can bring treatment of NMIBC from the inpatient to an outpatient office-based setup. Removal of small bladder tumours may be performed with diathermy in flexible cystoscopes under local anaesthesia. However, diathermy in local anaesthesia is

only offered to a limited number of patients with small, usually solitary, recurrences. The limitation of diathermy is pain perception, resulting in reduced patient tolerance of the procedure.

The LV technique has traditionally been tested using either a Holmium laser emitting light with a wavelength of 2100 nm or a Thulium laser emitting light with a wavelength of 2013 nm to vaporize the entire tumour.

Removal of bladder tumours using the Holmium laser technique may produce less pain than diathermia. However, the method has mainly been used for patients unfit for general anesthesia, presenting solitary or few small tumours and without routine simultaneous biopsy. Also, when using this technique, the operation procedure normally takes between 15 to 35 minutes, which may be straining for a fragile elderly awaken patient.

Conventionally laser treatment methods focus on vaporization. Laser TUR-BT has mainly been tested in rigid cystoscopes and in the operating theatre in general anesthetic using Holmium or Thulium lasers to vaporize the entire tumour or using vaporizing to do én-bloc tumour resection. The experience is that the operation time may be longer for laser surgery than conventional TUR-BT, but the method is safe, excellent hemostasis is achieved, obturator nerve reflection is not seen and bladder perforation very rare. With regard to recurrence rates, laser based TUR-BT is more or less equal to TUR-BT using diathermia.

Lately, Thulium laser TUR-BT of non-invasive urothelial bladder tumours in selected patients was reported showing a recurrence rate at 14.5% during 16 months follow-up and a 2 year over all recurrence rate at 48% after Holmium laser TUR-BT [Syed HA *et al*., J Endourol. 2013 July 27(7). pages 886-891]. Similar results may be found after golden standard TUR-BT in general anaesthetic but data comparing laser TUR-BT and conventional TUR-BT are missing.

There is thus need for a new and less invasive method for treating bladder cancer and bladder tumours.

Description of the invention

We present the use of a solid state light source based technique, which can replace repeated bladder tumour surgery of smaller tumours in the operating theatre with surgery without sedation and performed as outpatient department or office based procedures. A lot of resources can thus be spared for the patients and the health system. Further the treatment time is significantly.

Disclosed herein is in a first aspect of the invention a system for photo induced denaturation of tumour tissue inside the bladder in connection with treatment of bladder tumours.

The system comprises a first light source, the first light source being a solid state light source emitting light at a wavelength between 800-1000 nm or between 350-600 nm. The system further comprises a cystoscope comprising an endoscopic tube with a distal end adapted for extending through a patient's urethra into the patient's bladder, and a first optical transmission path for guiding light from the first light source to the distal end of the endoscopic tube.

The system also comprises a second light source emitting substantially monochromatic light with a predefined central wavelength between 500 and 550 nm, and a second optical transmission path for guiding light from the second light source to the distal end of the endoscopic tube.

Further comprised in the system is at least one optical band-rejection filter adapted to attenuate at least said second light source wavelength for a viewer by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB.

The first light source is adapted for photo induced denaturation of tumour tissue inside the bladder of the patient, and the second light source is adapted for illuminating at least a part of the patient's bladder by generating autofluorescence in tissue in the endogenous fluorophores in the bladder, and/or for inducing

fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD).

The first light source and the second light source are normally the only light sources in the system.

Disclosed herein in a second aspect of the invention is a method for treatment of bladder tumours by photo induced denaturation of tumour tissue inside the bladder, the method comprising the steps of:

- providing a system comprising:
  - a first light source being a solid state light source,
  - a cystoscope connected to the first light source, wherein the cystoscope comprises an endoscopic tube with a distal end,
  - a first optical transmission path for guiding light from the first light source to the distal end of the endoscopic tube, wherein the endoscopic tube is adapted to holding the first optical transmission path;
- introducing the distal end of the endoscopic tube into a bladder of a patient through the urethra of the patient, and
- illuminating the root area of bladder tumour tissue with light emitted from the first light source transmitted though the cystoscope to the distal end of the endoscopic tube such that photo induced denaturation of the root area of the bladder tumour tissue occurs thereby turning the bladder tumour into an ischemic tumour.

The advantages the above system and method is that the treatment of the patient:

- requires no anaesthetics, which makes it very suitable for use in outpatient settings
- only lasts a few minutes compared to 15-30 minutes by conventional laser surgery
- can be performed with lasers having a small size making it possible for the practitioner to carried them around in an office or outpatient setting

- can be implemented on existing endoscope/cystoscope systems using the biopsy channel of the endoscope to guide a fibre connected to the solid state light source
- is not dependent on the level of administrated photosensitizers, how well photosensitizer has migrated to the tumour area or if sufficient amounts of singlet oxygen is created in order to kill the tumour as is the case with photodynamic therapy (PDT)
- is not sensitive to the levels of oxygen in the tumours in contrast to PDT, which requires a minimum level of oxygen in order to obtain high enough levels of singlet oxygen for killing the tumour.

Brief description of the drawings

Figures 1a-c show in vitro results for diode laser treatment on chicken breast meat.

Figures 2a-e show in vivo results for diode laser treatment on a tumour in the bladder of a patient from the before treatment (figure 2a), during treatment (figure 2b), immediately after end treatment (figure 2c) and after end treatment (figures 2c-d).

Figure 3 shows a schematic illustration of two types of tumours in the bladder.

Figure 4 shows a very schematic illustration of the system.

Description of preferred embodiments

Throughout this description, photo induced denaturation of tumour tissue and de-vascularization of tumour tissue is used interchangeably.

Disclosed herein in a first aspect of the invention is a system for photo induced denaturation of tumour tissue inside the bladder in connection with treatment of bladder tumours. Figure 3 is a schematic illustration of a bladder 300 with three tumours 302, 304 inside the bladder wall and the urethra 306 leading into the bladder 300. Figure 4 is a schematic illustration of the system 400, where the size of the different items are not scaled in relation to one another.

The system 400 comprises a first light source 402, the first light source 402 being in one or more embodiments a solid state light source emitting light 404 at a wavelength between 800-1000 nm. This laser wavelength range is in particularly suitable for photo induced denaturation of tumour tissue having a cauliflower shape as shown as item 302 in figure 3.

Alternatively, the first light source 402 is in one or more embodiments a solid state light source emitting light at a wavelength between 350-600 nm. This laser wavelength range is in particularly suitable for photo induced denaturation of tumour tissue having a flat shape as shown as item 304 in figure 3.

The system 400 also comprises a cystoscope comprising an endoscopic tube 406 with a distal end 408 adapted for extending through a patient's urethra 306 into the patient's bladder 300 and a first optical transmission path 410 for guiding light 404 from the first light source 402 to the distal end 408 of the endoscopic tube 406. The first light source 402 is adapted for photo induced denaturation of tumour tissue 302, 304 inside the bladder 300 of the patient.

Disclosed in the system 400 is also a second light source 412 emitting substantially monochromatic light 414 with a predefined central wavelength between 500 and 550 nm, and a second optical transmission path 416 for guiding light from the second light source 412 to the distal end 408 of the endoscopic tube 406.

The second light source 412 is adapted for illuminating at least a part of the patient's bladder 300 by generating autofluorescence in tissue in the endogenous fluorophores in the bladder, and/or for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD). This ensures that the bladder 300 is illuminated enough for the practitioner to treat the tumour tissue 302, 304 inside the bladder 300 by means of the first light source 402.

The first light source 402 and the second light source 412 are the only light sources in the system 400.

Light reflected and/or emitted 418 from the bladder is collected and guided through the endoscopic tube to an electronic imaging device 420 allowing the surgeon to observe the region of interest in the bladder. A CCD camera may be used in this context.

Included in the system 400 may also be at least one optical band-rejection filter 422 adapted to attenuate at least said second light source wavelength 414 for a viewer by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB.

The system also comprises means for guiding the movement of the endoscopic tube when inserting the distal end 408 of the endoscopic tube 406 into the patient's bladder 300 through the patient's urethra 306 (hot shown in the figure) This is relevant when a flexible cystoscope is used.

In one or more embodiments, the first light source 402 is a diode laser, a high power light emitting diode, or a fibre laser. Other laser types may also be imagined.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 808 nm, 820 nm, 880 nm, 940 nm or 980 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 808 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 820 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 880 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 940 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 980 nm.

The conventionally used Holmium and Thulium lasers differs from the solid state light source used here as the first light source 402 in that the Holmium and Thulium lasers emit light at 2100 nm and 2013 nm, respectively, and not between 800-1000 nm or between 350-600 nm. At the infrared wavelengths of the Holmium and Thulium lasers, a strong optical absorption in water is present, which lead to a penetration depth of only 0.1 mm in water.

In the Holmium laser, being a pulsed laser, this leads to adiabatic heating of water and subsequent formation of steam bubbles, which ablate tissue mechanically but do not coagulate blood vessels. The continuous wave Thulium laser can coagulate blood vessels, but only if the fibre tip is in intimate contact with the blood vessel due to the strong absorbance of water at 2013 nm.

Thus, due to the very limited tissue penetration the Holmium and Thulium lasers, these laser cannot be used for de-vascularization as presented here.

An advantage of using a solid state light source in the form of e.g. a diode laser is the lack of steam bubble effect. Both the Holmium and the Thulium laser (however to less extent) creates steam bubbles, when their energy destructs the tissue which may affect visibility during the operation. Another advantages of solid state light sources in comparison with Holmium and Thulium lasers are a smaller box size and a much higher wall-plug efficiency i.e., how much of the main supply is converted into laser power and a lower price.

In this invention, photo induced denaturation / de-vascularization of the tumour by illuminating the blood vessels in the tumour base / root 308 with a wavelength between 800-1000 nm, which is absorbed in haemoglobin, results in a heating of haemoglobin. The accumulated heat in the haemoglobin and surrounding tissue cause clotting of the vessels and subsequent tumour ischemia. The tumour 302, 304 is not removed from the bladder 300 during the procedure, but exfoliates during the

following days due to ischemia. Patients tell that they pass small tissue clots in the urine during days after treatment.

At one of the wavelength ranges used in this invention, i.e. 800-1000 nm, haemoglobin absorbs light efficiently, which results in an occluded vessels in the tumour base. At e.g. 980 nm the optical absorption coefficient in hemoglobin is 50 cm^{-1}, which is sufficient to heat and ensure coagulation of blood vessels in tumour. Furthermore, a low absorption coefficient of 0,3 cm^{-1} in water makes deep tissue penetration possible.

Shorter wavelengths absorbed more strongly by haemoglobin could also be used to treat carcinoma in situ of the bladder wall in order to prevent unintended heating of healthy tissue below which may cause pain.

Normally, wavelengths in blue spectral region are avoided for photocoagulation in medical treatments of the retina and skin diseases like telangiectasia and haemangioma. In the case of the retina it is to avoid absorption in xanthophyll (pigment of the macula). For treatment of skin diseases the blue laser light would be scattered too strongly (due to Rayleigh and Lorenz-Mie scattering).

The use of blue light for photocoagulation of blood vessels in tumour 302, 304 of the bladder may therefore be unique to the bladder. The first light source 402 may therefore emit light 404 at a wavelength of between 350-600 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 350-500 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 350-500 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 400-500 nm.

In one or more embodiments, the first light source 402 is a frequency doubled Nd:YAG proving frequency doubled light at 532 nm.

To limit stimulation of pain nerve fibres, a short pulse duration provided in intervals is normally used. The procedure most often provides basically no pain for the patient.

In one or more embodiments, the first light source 402 is a laser emitting a pulse with a duration of approximately 1 millisecond.

In one or more embodiments, the first light source 402 is a laser emitting a pulse in intervals of 1-10 milliseconds.

In one or more embodiments, the first light source 402 is a laser emitting a pulse in intervals of 3-7 milliseconds.

In one or more embodiments, the first light source 402 is a laser emitting a pulse in intervals of 4-5 milliseconds.

In one or more embodiments, the first light source 402 is a laser emitting a pulse with a duration of approximately 1-10 millisecond and in intervals of 1-10 milliseconds.

In one or more embodiments, the first light source 402 is emitting pulses for an exposure treatment time of between 10-240 seconds, or between 10-120 seconds, or between 30-120 seconds, or between 30-60 seconds is used.

Normally, only the base 308 of the tumour 302, 304, and not the entire tumour is denaturized. A tumour up to a size of about 2 centimetres may be de-vascularize using a solid state light source between 800-1000 nm or 350-600 nm according to this invention. The de-vascularized tumour 302, 304 is left in the bladder 300 after treatment. As the tumour 302, 304 is left in situ but without blood supply, it will become necrotic (i.e. it will die) and fall off after some weeks. The tumour 302 ,304 then exfoliates due to ischemia.

Most suitable for removing papillary carcinomas (cauliflower-shaped tumours) 302 using photo denaturisation is a solid state light source between 800-1000 nm, whereas the flat carcinomas like carcinoma in situ (CIS) 304 are best removed used photo denaturisation with a solid state light source between 350-600 nm.

The procedure is almost pain free and do not include the use of anaesthetic. Normally, the patients can leave the outpatient department immediately after the cystoscope has been removed.

The first light source 402 is used in combination with a system comprising a cystoscope comprising an endoscopic tube 406 with a distal end 408 adapted for extending through a patient's urethra into the patient's bladder, the endoscopic tube 406 being adapted to hold a first optical transmission path 410 for guiding light from the solid state light source, i.e. the first light source 402, to the distal end 408 of the endoscopic tube 406, and means for guiding the movement of the endoscopic tube when inserting the distal end of the endoscopic tube into the patient's bladder through the patient's urethra.

In one or more embodiments, the cystoscope is a flexible cystoscope.

In one or more embodiments, the cystoscope comprises biopsy extracting means adapted for extraction a biopsy sample from the bladder, wherein the biopsy extracting means extends into the patient's bladder through the endoscopic tube.

When photo induced denaturation of tumor tissue inside the bladder of the patient is performed means which can illuminate the bladder will normally be present. The system 400 therefore normally comprises illumination means adapted for monitoring the bladder tissue during the photo induced denaturation of tumour tissue inside the bladder of the patient. The illumination means are either white light illumination or a light adapted for inducing autofluorescence in tissue in the endogenous fluorophores in the bladder, and/or for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD).

A common problem encountered in endoscopic examination of bladders is that urine has a relatively strong absorption in the UV-blue region. Many commercial monochromatic light sources, used for photodynamic diagnosis or other methods for visualizing malignant tissue, emit light in the UV-blue region and thus cause strong green fluorescence in urine that confounds the sensitized fluorescence of the malignant tissue. As urine enters the bladder constantly during examination this problem cannot be avoided and prevents the use of photodynamic diagnosis for bladder cancer to be used in the outpatient department (OPD). Normally an endoscope utilizes two wavelength bands, one bright white light source used for illuminating the bladder with white light and a narrow band of light obtained by optically filtering the white light source for exciting the fluorophore of the photosensitizer. The physician locates the pre-cancerous tissue with the fluorescent light and switches to white light in order to remove the pre-cancerous tissue surgically. Thus, the physician has to switch between the two light sources during examination.

Another problem encountered in diagnostic methods based on fluorescent labeling and photodynamic diagnosis of pre-cancerous tissue in the bladder is photobleaching of the fluorophores used for labeling. Photobleaching is primarily caused by bright blue light sources used for illuminating the bladder. The consequence is that some precancerous tissues may remain undetected by the physician.

The system and the method of the present disclosure need only have one light source for illuminating the bladder during photo induced denaturation of tumour tissue inside the bladder of the patient, since the monochromatic second light source generates sufficient autofluorescence in the bladder to allow an observer, e.g. a physician, to view the tissue irradiated by the light from the monochromatic second light source because the irradiated tissue is being illuminated by the autofluorescence generated in the irradiated tissue, i.e. the tissue fluoresces whereby it becomes visible.

In an embodiment of the invention, the illumination means is in the form of a second light source 412 emitting substantially monochromatic light with a predefined central wavelength between 500 and 550 nm combined with a second optical transmission path 416 for guiding light 414 from the second light source 412 to the distal end 408 of the endoscopic tube 406. The first 410 and the second transmission path 416 may be combined or two separate channels extending through the endoscopic tube 406.

Bladder cancer is identified and resected during endoscopic examination of the bladder through the urethra. A new kind of photodynamic diagnosis (PDD) of bladder cancer (BC) was developed in 2001 where hexaminolevulinate or 5-aminolevulinic acid (5- ALA) is used as precursor to the dye. The aminoacid 5-ALA is metabolized to protoporphyrin IX (PPIX) in the malignant cells which fluoresces at approx. 635 nm when excited with blue light. However, a problem with this procedure is that yellow urine in the bladder is also excited by the blue light to generate strong green fluorescence. This confounds the fluorescence and the vision in the bladder becomes heavily impaired by the green fluorescence and thus the diagnosis of the malignant tissue.

By instead using light with wavelengths greater than 500 nm and less than 550 nm, fluorescence from urine is avoided at the same time as enough autofluorescence from the bladder wall is obtained for the practitioner to obtain a clear view of the bladder wall and to further observe fluorescence from a photosensitive compound accumulated in precancerous, malignant and/or fast-growing cells in the bladder.

The photosensitive compound used here is preferably selected from the group of porphyrins, such as haematoporphyrin or protoporphyrin, preferably protoporphyrin IX (PPIX). The photosensitive compound is preferably delivered to malignant cells by means of a precursor based on levulinic acid, such as hexaminolevulinate (e.g. Hexvix(R)), 5-aminolevulinic acid (ALA or 5-ALA) or methyl aminolaevulinate (MAL, e.g. Metvix). Levulinic acid are metabolized to photosensitive PPIX in cells through the intrinsic cellular haem biosynthetic pathway.

In one or more embodiment of the invention the second light source 412 is a laser, such as a fibre coupled laser, a fibre laser, a solid state laser, a diode pumped solid state laser, a light emitting diode (LED) or a semiconductor laser. The second light source 412 may be adapted to emit continuous wave (CW) light.

A laser light source as the second light source 412 has the advantage that it can be directed from an external location to the distal end 408 of endoscopic tube 406 through a very thin optical fiber thereby minimizing the cross-sectional area of the cystoscope. When using a fiber for guiding the light, the light out of the cystoscope will exit the fiber spreading out in a cone of light out irradiating a large portion of the tissue.

The substantially monochromatic second light source 412 may have an emission spectrum with a FWHM of between 1 and 50 nm, thereby approx. ranging from a laser source to an LED. Thus, in a further embodiment the emission spectrum of the substantially monochromatic light source has a FWHM of less than 50 nm, or less than 45 nm, or less than 40 nm, or less than 35 nm, or less than 30 nm, or less than 25 nm, or less than 20 nm, or less than 15 nm, or less than 10 nm, or less than 8 nm, or less than 6 nm, or less than 4 nm, or less than 3 nm, or less than 2 nm, or less than 1 nm.

When using an LED it may be an advantage to combine with a bandpass filter 424 to narrow the emission spectrum of the second light source. The FWHM of the unfiltered LED is approx. 40 nm, however the spectrum of the LED actually covers a span from 450 nm to 600 nm. This may not be desirable because the "blue" 450-500 nm range is possibly unwanted due to stimulation of green fluorescence from e.g. urine and the "red" 550-600 nm range will confound the native fluorescence of the tissue.

Consequently a bandpass filter 424 can be inserted, e.g. in the optical path between the second light source and the cystoscope. The bandpass filter reduces the FWHM to approx. 25 nm thereby reducing the lower wavelength light that may induce fluorescence in e.g. urine and also reducing the longer wavelength light that may be

allowed through the band-rejection filter, i.e. the filter maximises the desired sensitized fluorescence from cancerous tissue as well as the native autofluorescence of the healthy tissue.

A further advantage of a bandpass filter 424 is that it may be designed so that the bandpass filter for the second light source and the band-rejection filter 422 for the viewer are adapted to match each other closely, however preferably with no overlap between the two filters.

The predefined central wavelength of the second light source may be between 500 and 505 nm, or between 505 and 510 nm, or between 510 and 515 nm, or between 515 and 520 nm, or between 520 and 530 nm, or approx. 525 nm, or between 525 and 530 nm, or between 530 and 535 nm, or between 535 and 540 nm, or between 540 and 545 nm, or between 545 and 550 nm.

At least one optical band-rejection filter adapted to attenuate the illumination light 414 from the second light source 412 is normally included in the system 400 for photo induced denaturation of tumour tissue inside the bladder according to the present disclosure.

The band-rejection filter may be a narrow band rejection filter, such as a notch filter, preferably a Raman notch filter, also known as a rugate filter. Another example of a narrow band rejection filter that can be used is a Fabry-Perot etalon. In the preferred embodiment of the invention the rejection band of the band-rejection filter comprises the second light source wavelength; preferably the rejection band of the band-rejection filter is centred on the central second light source wavelength.

The rejection band of the filter may be less than 20 nm, more preferably less than 15 nm, more preferably less than 12 nm, more preferably less than 10 nm, more preferably less than 8 nm, more preferably less than 6 nm, more preferably less than 4 nm, more preferably less than 2 nm.

The band-rejection filter may also be designed such that it blocks wavelengths below around the central wavelength of the monochromatic light source and allows wavelengths above this wavelength.

The band-rejection filter is preferably adapted to attenuate said light source wavelength by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB.

The inventors have observed that the combination of a monochromatic light source (such as a laser light or LED source) and the band rejection filter, preferably a narrow band notch filter, allows the surgeon to use the autofluorescence of the surrounding (healthy) tissue as normal examination light, because the irradiated tissue fluoresces and thereby becomes visible. In an example a 532 nm laser was used, in another example a 525 nm LED was used resulting in an autofluorescence spectrum from surrounding tissue of approx. 550-700 nm, i.e. only the green, yellow and red part of the visible spectrum, but still adequate for discerning the morphology of the tissue. Using the monochromatic light source generated autofluorescence light from the healthy tissue as normal examination light allows the surgeon to skip the use of bulky liquid core light guides and power consuming metal halide lamps or discharge lamps, like xenon lamps, normally used in many endoscopic procedures. Use of a laser or LED as examination light source greatly reduces the footprint of the optical transmission path, because the laser light may be transmitted to the region of examination via a thin optical fiber with a diameter of 0.5 mm. And the power consumption of the excitation light source may also be reduced.

In one or more embodiments, a first fibre is connected to or part of the first light source, the first fibre extending through the endoscopic tube when the cystoscope and the first light source are connected.

Likewise, in one or more embodiments, a second fibre is connected to the or part of the second light source, the second fibre extending through the endoscopic tube when the cystoscope and the second light source are connected.

In one or more embodiments, the cystoscope further comprises biopsy extracting means adapted for extraction a biopsy sample from the bladder, wherein the biopsy extracting means extends into the patient's bladder through an auxiliary channel in the endoscopic tube.

In one or more embodiment, the cystoscope is a digital cystoscope.

In one or more embodiment, the cystoscope is made from a material which can be reused.

The system for photo induced denaturation of tumour tissue inside the bladder may be incorporated in endoscopes/cystoscopes with eyepieces with the band-rejection filter placed in front of the eyepiece or somewhere in the optical relay system, in endoscopes where the monitoring is provided via monitors/display and provided by means of a camera, with the band- rejection filter placed in front of the camera or the CCD of the camera.

The illumination system according to the present disclosure may be incorporated in (digital) endoscopes where the imaging device (e.g. a CCD) is located at the distal end of the endoscope. The band-rejection filter is then normally placed in front of the imaging device.

The possibility to perform photodynamic diagnosis of bladder cancer in the outpatient department combined with photo induced denaturation of tumour tissue inside the bladder of the patient greatly reduces the cost of bladder cancer / tumor diagnosis and treatment.

In a second aspect of this invention is disclosed a method for treatment of bladder tumours by photo induced denaturation of tumour tissue inside the bladder. The method comprising the steps of:

- providing a system comprising:
    - a first light source being a solid state light source, and
    - a cystoscope connected to the first light source, wherein the cystoscope comprises an endoscopic tube with a distal end,

- a first optical transmission path for guiding light from the first light source to the distal end of the endoscopic tube, wherein the endoscopic tube is adapted to holding the first optical transmission path;

- introducing the distal end of the endoscopic tube into a bladder of a patient through the urethra of the patient, and
- illuminating the root area of bladder tumour tissue with light emitted from the first light source transmitted though the cystoscope to the distal end of the endoscopic tube such that photo induced denaturation of the root area of the bladder tumour tissue occurs thereby turning the bladder tumour into an ischemic tumour.

The method may further comprise the step of removing the endoscopic tube from the patient after end treatment of the root area of the bladder tumour tissue leaving the ischemic tumour inside the bladder of the patient.

In one or more embodiments, the photo induced denaturation of tumour tissue extends to a penetration depths between 1-6 mm below the surface of the bladder wall.

In one or more embodiments, the first light source is a diode laser, a high power light emitting diode, or a fibre laser.

In one or more embodiments of the method, the first light source may be a diode laser emitting light at a wavelength between 800-1000 nm.

In one or more embodiments of the method or the system, the first light source may be one of the following laser types:

- a diode laser
- a diode laser emitting light at a wavelength of 808 nm
- a diode laser emitting light at a wavelength of 820 nm
- a diode laser emitting light at a wavelength of 880 nm
- a diode laser emitting light at a wavelength of 940 nm
- a diode laser emitting light at a wavelength of 980 nm
- a high power light emitting diode

- a fibre laser.

In one or more embodiments, the treatment time for illuminating the root area of bladder tumour tissue with light from the solid state light source is between 10-240 seconds, or between 10-120 seconds, or between 30-120 seconds, or between 30-60 seconds.

In one or more embodiments of the method, the first light source is a diode laser emitting light at a wavelength between 350-600 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 350-500 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 350-500 nm.

In one or more embodiments, the first light source 402 is a diode laser emitting light at a wavelength of 400-500 nm.

In one or more embodiments, the first light source 402 is a frequency doubled Nd:YAG proving frequency doubled light at 532 nm.

In one or more embodiments of the method, the cystoscope is a flexible cystoscope.

In one or more embodiments of the method, the cystoscope is a digital cystoscope.

In one or more embodiments of the method, the method further comprises the step of extracting a biopsy sample from the patient's bladder through an auxiliary channel in the endoscopic tube.

In one or more embodiments of the method, the method further comprises the step of monitoring the bladder tissue during the photo induced denaturation of tumour tissue inside the bladder of the patient by using a second light source extending through a second optical transmission path for guiding light from the second light

source to the distal end of the endoscopic tube, wherein the second light source is adapted for illuminating at least a part of the patient's bladder by generating autofluorescence in tissue in the endogenous fluorophores in the bladder, and/or for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD).

In one or more embodiments of the method, the light adapted for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD) has a central wavelength between 500-550 nm.

In one or more embodiments of the method, a first fibre is connected to or part of the first light source, the fibre extending through the endoscopic tube when the cystoscope and the first light source are connected.

In one or more embodiments of the method, the cystoscope is made from a material which can be reused.

In one or more embodiments of the method, the method further comprises the step of disposing of the cystoscope after use thereby only using the cystoscope for treatment of one single patient.

The possibility to perform photodynamic diagnosis of bladder cancer in the outpatient department combined with photo induced denaturation of tumour tissue inside the bladder of the patient greatly reduces the cost of bladder cancer / tumor diagnosis and treatment.

An in vitro model has also been developed to examine dose/response relation between the laser power, treatment time and distance between a fibre connected to a diode laser and the target-on-tissue destructive effect. The method has also been tested used in vivo in patients with low grade stage Ta tumours.

In vitro experiments

An in vitro model was developed to achieve knowledge on dose and response relation between diode laser treatment and tissue destructive effect. The impact of varying laser illumination time, laser power and distance between fibre and target tissue were investigated.

To achieve knowledge on a dose/response relation between laser treatment time and tissue destructive effect, an in vitro model was developed where exact distance between the fibre from where the diode laser light emanates and the chicken breast meat lowered in the 37 Celsius degrees hot water. Water temperature was continuously monitored.

The laser treatment with a diode laser emitting light at 980 nm in 1 millisecond pulses at intervals of 1 millisecond was conducted for 10 seconds, 15 seconds, 30 seconds and 45 seconds. The 980 nm diode laser was set to an average power of 12 W. The diode laser was a 220 V / battery driven laser with a green 532 nm aiming beam and a front firing 400 µm 0,22 numerical aperture bare laser fibre attached (Fox Laser; dimensions: 14 x 16 x 17 cm and 1.2 kilo; A.R.C. Laser GmbH, Nüremberg. Germany).

The distance between the chicken meat and a fibre connected to the diode laser for controlling the illumination distance between the laser light and the chicken meat was set to 0 mm, the fibre just touching the meat without applying pressure to the chicken meat. Figure 1a shows the laser induced tissue destruction in chicken meat after 45 seconds of laser illumination.

Depth and width of tissue coagulation/vaporization was measured in 5 mm wide and 10 mm deep biopsies from the chicken breast meat. The biopsies were examined in a microscope and the depth and width of the tissue coagulation/vaporization was detected. A stereo-microscope (Olympus SZ61, Olympus, Tokyo, Japan; light source: Intralux® 4100, Volpi, Auburn, NY) was used. Bright field images were captured using a camera mounted to the microscope (ProgRes, CT3 USB, Jenoptik, Jena, Germany) and depth and width of tissue coagulation/vaporization was measured with associated software (ProgRes CapturePro v. 2.8.8, Jenoptik, Jena, Germany).

Measurements were done six times per period. Each experiment was done six times and results presented as median and quartiles. Pearson´s correlation coefficient, r, was calculated to evaluate correlation between duration of laser illumination time and magnitude of tissue destruction.

Figure 1b shows the tissue destruction depth as a function of the laser treatment time and figure 1c shows the tissue destruction width as a function of the laser treatment time. From figure 1b it can be seen that the destructive effect in depth appears to reach a maximal effect after between 30 to 45 seconds. Contrary, the width of the tissue destruction as shown in figure 1c seems to have a constant level between 2-3 millimetre.

Table 1 summarizes the results in figure 1b and 1c. Pearson´s r correlation coefficient for illumination time and depth of tissue destruction was 0.84 ($P<0.0001$) The destructive effect appears to reach a near maximum of 4.1 mm after 30 seconds of laser illumination after which the tissue destruction levels off. The width of tissue destruction appeared less related with illumination time being between 2-3 mm (Table 1; $r= 0.71$; $P<0.0001$).

Table 1. Relation between duration of laser illumination time and magnitude of tissue destruction.

Laser illumination time (seconds)	Depth of tissue destruction (µm, n=6 samples)			Width of tissue destruction (µm, n=6 samples)		
	Median	25% quartile	75% quartile	Median	25% quartile	75% quartile
10	2472	1847	2533	1987	1807	2091
15	2920	2575	3216	1861	1681	2091
30	4113	3922	4485	3080	2577	3366
45	4487	4225	4623	2807	2671	3138

To evaluate the influence of greater distance between laser fibre tip and target on tissue destructive effect, six tests were performed using 2 mm distance and laser

illumination for 30 sec. These settings reduced the median depth of tissue destruction from 4.1 mm to 1.5 mm and the median width from 3.0 mm to 1.7 mm. The distance of 2 mm mimics the clinical situation when we treat bladder tumours.

The in vitro results of the depth of penetration of energy into chicken meet presented in figures 1b, is in accord with the absorption spectrum of prevailing body chromophores and related tissue penetration.

Measurements of tissue penetration to the side (see figure 1c), has to our knowledge not been presented before. Tissue penetration next to the laser fibre is important knowledge as treatment may involve laser activity having the fibre placed parallel and close to the adjacent bladder wall. Knowing that the laser do not harm adjacent tissue next to the fibre deeper than 2-3 mm and thus do not penetrate the bladder wall makes this procedure much safer than the conventional laser based treatment methods. It may even secure that tumour tissue below the mucosa is destroyed and thus exert a clinical effect.

In vivo experiments

In the in vivo experiments, a flexible cystoscope (Karl Storz) was used through which a 400 micron fibre was introduced into the bladder through the urethra.

Figure 2a-e show the inside of a bladder in a 62 years old male patient with a previous history of Ta low grade urothelial tumour at different time during treatment of bladder cancer. As can be seen in the before treatment picture in figure 2a, the patient has healthy tissue 200 and – before treatment – a 1.5 cm partly broad based tumour 202. Figure 2b is a picture taken during the treatment period and figure 2c is taken directly after the treatment has ended. In figure 2c, it can be seen that the tumour 200 is still attached to the healthy tissue 200.

The laser treatment procedure shown in figure 2a-c lasted two minutes and the entire procedure including a washing lasted for about 15 minutes. Afterwards, the patient could leave the OPO for returning to work.

The alternative standard treatment would require one to three days of hospitalization and surgery during general anaesthesia.

The diode laser in the in vivo studies was used with similar settings as for the in vitro studies. The tumour was given laser treatment for a total of two minutes at different places at tumour basis and the tumour was left in situ.

Biopsy and images of the tumour area shown in figure 2a-c was observed again 14 days and 4 months after treatment as shown in figure 2d and figure 2e, respectively. As can be seen in figure 2d no residual tumour was detected after 14 days – only a small reddening 204 of the treated tissue area is observable when comparing figure 2d and figure 2e.

During the entire laser treatment, saline was used to distend the bladder. No sedatives or pain treatment was given. The patient was awake and saw the treatment on a screen. Pain score was 0 on a visual log scale from 0-10 where 10 is maximal pain.

The complete disappearance of the tumour two weeks later end treatment (see figure 2d), was measured using photodynamic diagnosis (PDD; Hexvix; Photocure ASA, Oslo, Norway) guided cystoscopy performed in the operating theatre using a rigid cystoscope and having the patient in general anesthesia (Figure 2d). Biopsies from the tumour area comprised inflammatory tissue and no neoplasia.

Four months after the laser TUR-BT a PDD guided cystoscopy using a flexible cystoscope (PDD 11272 VPI, D-Light C Light source; Karl Storz, Tuttlingen, Germany) was performed in the OPD (see figure 2e). No recurrence but a scar was observed at the previous tumour place, and biopsy from the area comprised no dysplasia or tumour (Figure 2e).

Tumours all over the bladder may be treated using the setup described herein, even in the bladder neck when using a flexible cystoscope with endoscopic tubes in the form of smooth and bendable laser fibres.

The larger the tumour volume is, the more convenient is the de-vascularization method of this invention if the base can be addressed. The largest tumour size for treatment normally does not exceed 2-2.5 cm, but the number of tumours to be treated in one patient is less important. We have treated up to 10 tumours in a bladder of one patient may be treated during one treatment session.

To limit stimulation of pain nerve fibres, we used short pulse duration of 1 milliseconds with intervals of 1 milliseconds. This laser setting only gives minor pain and is for many patients painless. Pain score was in our patients between 0-3 on the visual analogue pain scale ranging from 0–10. Laser treatment on flat carcinoma in situ identified with PDD was more painful than treatment of exorphytic tumours. This phenomenon may be due to normal nerve supply in flat dysplastic mucosa in contrast to tumours.

References

200	healthy tissue
202	tumour
204	treated tissue area after the tumour has fallen off the bladder wall
300	bladder
302	cauliflower-shaped tumour
304	flat tumour
306	urethra
308	tumour base / root
400	system for photo induced denaturation of tumour tissue
402	first light source
404	light from the first light source
406	endoscopic tube
408	distal end of the endoscopic tube
410	first optical transmission path
412	second light source
414	light from the second light source
416	second optical transmission path
418	light reflected and/or emitted from the bladder
420	unit for viewing the reflected/emitted light
422	band-rejection filter
424	bandpass filter

Claims

1. System for photo induced denaturation of tumour tissue inside the bladder in connection with treatment of bladder tumours, the system comprising:

   - a first light source, the first light source being a solid state light source emitting light at a wavelength between 800-1000 nm or between 350-600 nm;
   - a cystoscope comprising an endoscopic tube with a distal end adapted for extending through a patient's urethra into the patient's bladder;
   - a first optical transmission path for guiding light from the first light source to the distal end of the endoscopic tube;
   - a second light source emitting substantially monochromatic light with a predefined central wavelength between 500 and 550 nm;
   - a second optical transmission path for guiding light from the second light source to the distal end of the endoscopic tube, and
   - at least one optical band-rejection filter adapted to attenuate at least said second light source wavelength for a viewer by more than 10 dB, preferably by more than 20 dB, preferably by more than 30 dB, preferably by more than 40 dB, preferably by more than 50 dB, most preferably by more than 60 dB,

   wherein the first light source is adapted for photo induced denaturation of tumour tissue inside the bladder of the patient, and

   wherein the second light source is adapted for illuminating at least a part of the patient's bladder by generating autofluorescence in tissue in the endogenous fluorophores in the bladder, and/or for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD), and

   wherein the first light source and the second light source are the only light sources in the system.

2. System according to claim 1, wherein the first light source is a diode laser, a high power light emitting diode, or a fibre laser.

3. System according to any preceding claim, wherein the first light source is a diode laser emitting light at a wavelength of 808 nm, 820 nm, 880 nm, 940 nm or 980 nm.

4. System according to any preceding claim, wherein the first light source is a laser emitting a pulse with a duration of 1-10 milliseconds.

5. System according to any preceding claim, wherein the first light source is a laser emitting a pulse in intervals of 1-10 milliseconds.

6. System according to any preceding claim, wherein the first light source is a laser emitting a pulse with a duration of approximately 1-10 millisecond in intervals of 1-10 milliseconds.

7. System according to any preceding claim, wherein the cystoscope is a flexible cystoscope.

8. System according to claim 7 further comprising means for guiding the movement of the endoscopic tube when inserting the distal end of the endoscopic tube into the patient's bladder through the patient's urethra.

9. System according to any preceding claim, wherein the cystoscope further comprises biopsy extracting means adapted for extraction a biopsy sample from the bladder, wherein the biopsy extracting means extends into the patient's bladder through an auxiliary channel in the endoscopic tube.

10. System according to any preceding claim, wherein the first light source is emitting pulses for an exposure treatment time of between 10-240 seconds, or between 10-120 seconds, or between 30-120 seconds, or between 30-60 seconds is used.

11. System according to any preceding claim, wherein a first fibre is connected to or part of the first light source, the first fibre extending through the endoscopic tube when the cystoscope and the first light source are connected.

12. System according to any preceding claim, wherein a second fibre is connected to or part of the second light source, the second fibre extending through the endoscopic tube when the cystoscope and the second light source are connected.

13. System according to any preceding claim, wherein the cystoscope is a digital cystoscope.

14. System according to any preceding claim, wherein the cystoscope is made from a material which can be reused.

15. Method for treatment of bladder tumours by photo induced denaturation of tumour tissue inside the bladder, the method comprising the steps of:

- providing a system comprising:
  - a first light source being a solid state light source, and
  - a cystoscope connected to the first light source, wherein the cystoscope comprises an endoscopic tube with a distal end,
  - a first optical transmission path for guiding light from the first light source to the distal end of the endoscopic tube, wherein the endoscopic tube is adapted to holding the first optical transmission path;
- introducing the distal end of the endoscopic tube into a bladder of a patient through the urethra of the patient, and
- illuminating the root area of bladder tumour tissue with light emitted from the first light source transmitted though the cystoscope to the distal end of the endoscopic tube such that photo induced denaturation of the root area of the bladder tumour tissue occurs thereby turning the bladder tumour into an ischemic tumour.

16. Method according to claim 15 further comprising the step of removing the endoscopic tube from the patient after end treatment of the root area of the bladder tumour tissue leaving the ischemic tumour inside the bladder of the patient.

17. Method according to any one of the claims 15-16, wherein the treatment time for illuminating the root area of bladder tumour tissue with light from the first light source is between 10-240 seconds, or between 10-120 seconds, or between 30-120 seconds, or between 30-60 seconds.

18. Method according to any one of the claims 15-17, wherein the first light source is a diode laser, a high power light emitting diode, or a fibre laser.

19. Method according to any one of the claims 15-18, wherein the first light source is a diode laser emitting light at a wavelength between 800-1000 nm.

20. Method according to any one of the claims 15-19, wherein the first light source is a diode laser emitting light at a wavelength of 808 nm, 820 nm, 880 nm, 940 nm or 980 nm.

21. Method according to any one of the claims 15-20, wherein photo induced denaturation of tumour tissue extends to a penetration depths between 1-6 mm below the surface of the bladder wall.

22. Method according to any one of the claims 15-18, wherein the first light source is a diode laser emitting light at a wavelength between 350-600 nm.

23. Method according to claim 22, wherein photo induced denaturation of tumour tissue extends to a penetration depths between 0.1-1 mm below the surface of the bladder wall.

24. Method according to any one of the claims 15-23, wherein the cystoscope is a flexible cystoscope.

25. Method according to any one of the claims 15-24, wherein the cystoscope is a digital cystoscope.

26. Method according to any one of the claims 15-25 further comprising the step of extracting a biopsy sample from the patient's bladder through an auxiliary channel in the endoscopic tube.

27. Method according to any one of the claims 15-26 further comprising the step of monitoring the bladder tissue during the photo induced denaturation of tumour tissue inside the bladder of the patient by using a second light source extending through a second optical transmission path for guiding light from the second light source to the distal end of the endoscopic tube, wherein the second light source is adapted for illuminating at least a part of the patient's bladder by generating autofluorescence in tissue in the endogenous fluorophores in the bladder, and/or for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD).

28. Method according to claim 27 wherein the light adapted for inducing fluorescence in exogenous fluorophores administrated to the patient prior to treatment for performing photodynamic diagnosis (PDD) has a central wavelength between 500-550 nm.

29. Method according to any one of the claims 15-28 wherein a first fibre is connected to or part of the first light source, the fibre extending through the endoscopic tube when the cystoscope and the first light source are connected.

30. Method according to any one of the claims 15-29 wherein the cystoscope is made from a material which can be reused.

31. Method according to any one of the claims 15-30 further comprising the step of disposing of the cystoscope after use thereby only using the cystoscope for treatment of one single patient.

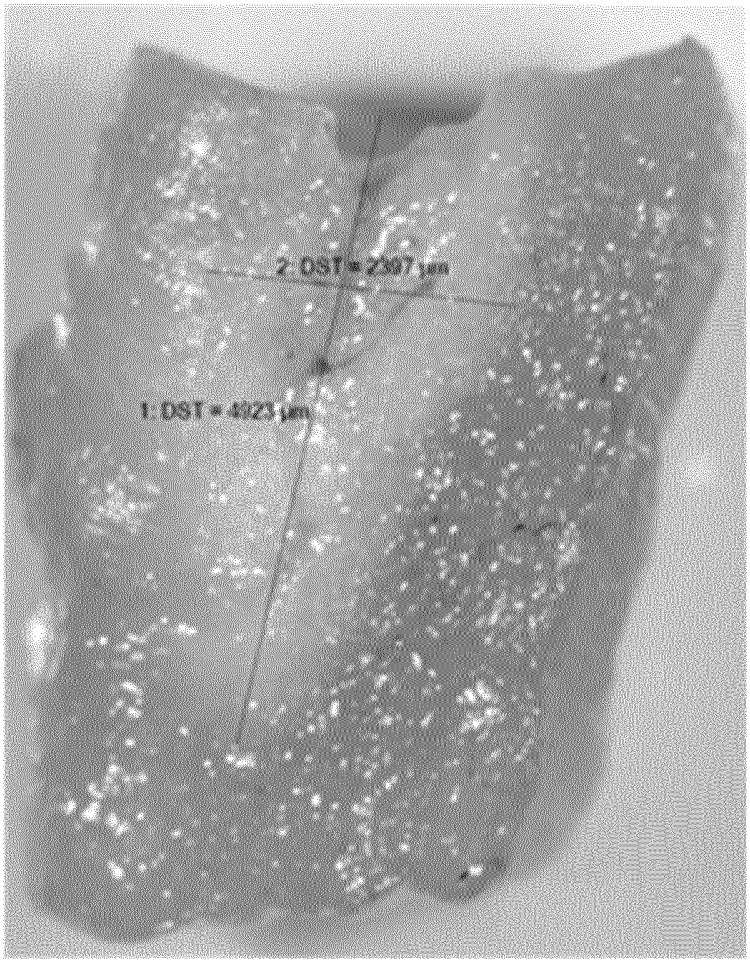
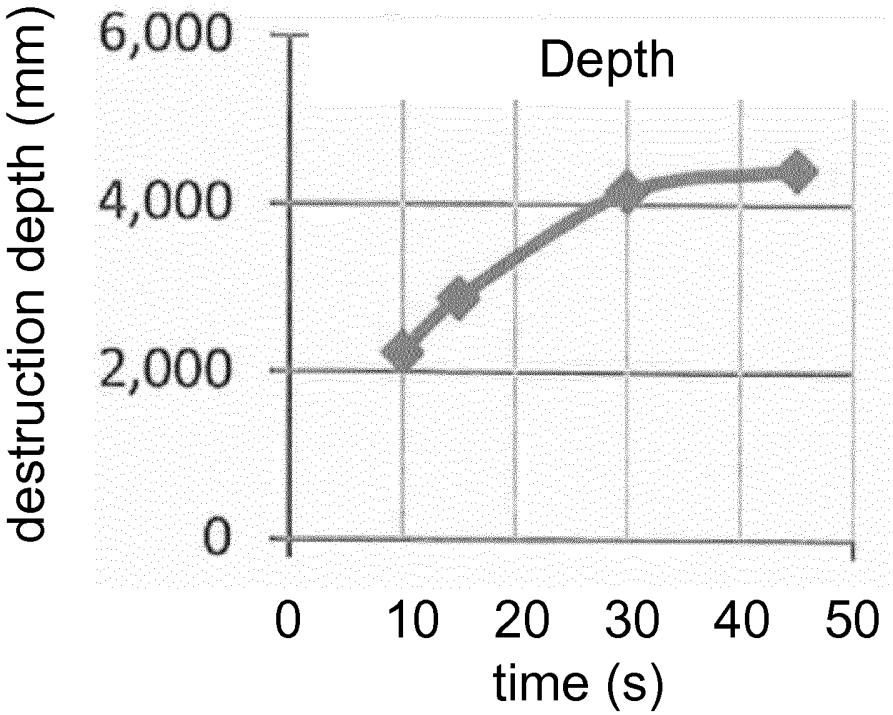


Fig. 1a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10
20
30
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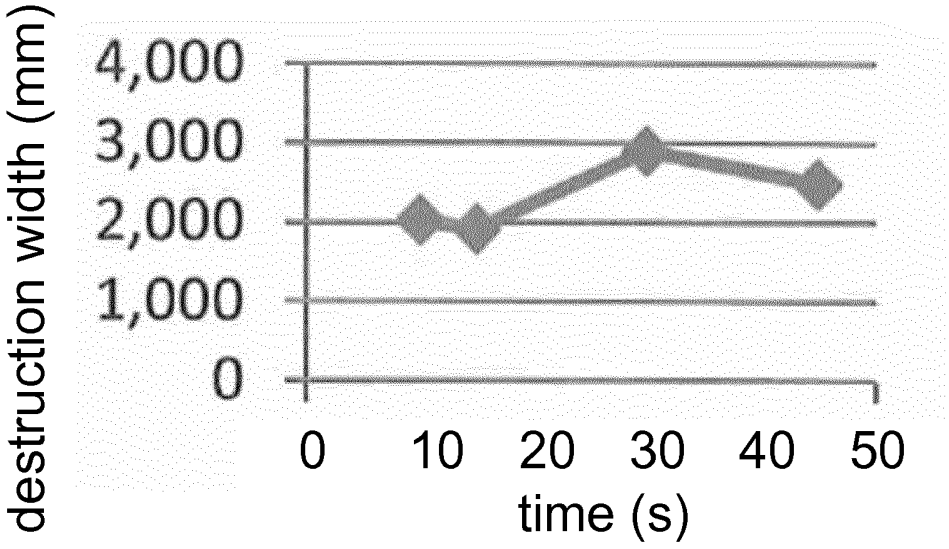
50
time (s)

Fig. 1b


destruction width (mm)
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1,000
0
0
10
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40
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time (s)

Fig. 1c

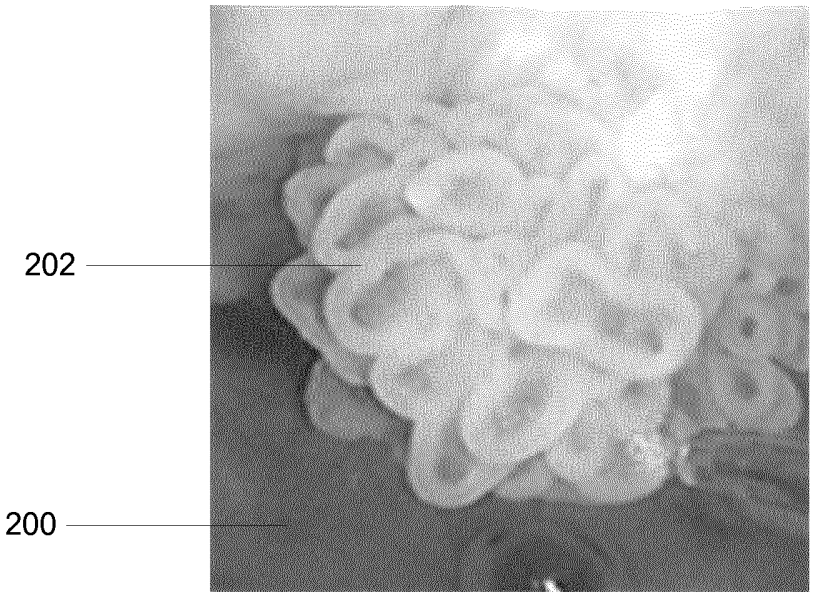

Fig. 2a

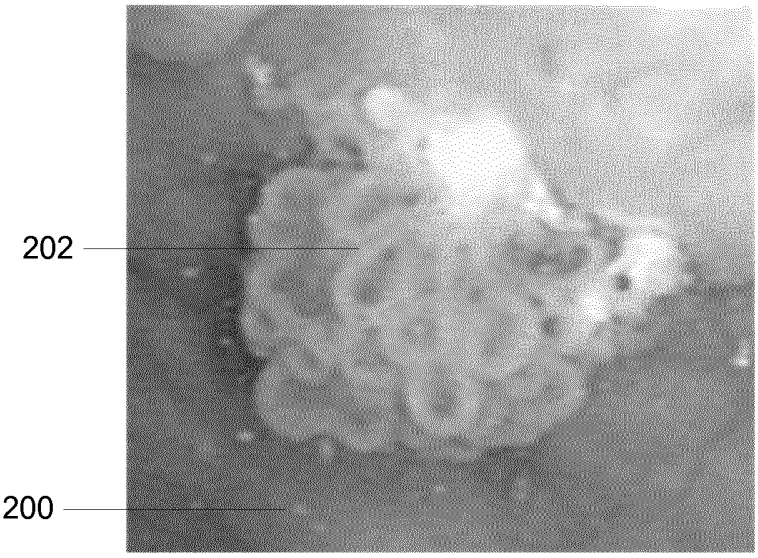

Fig. 2b

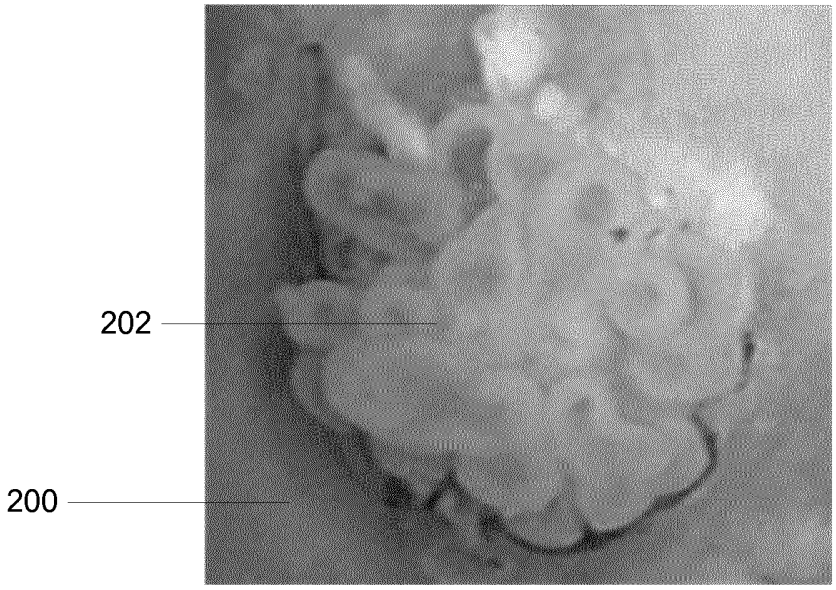

Fig. 2c

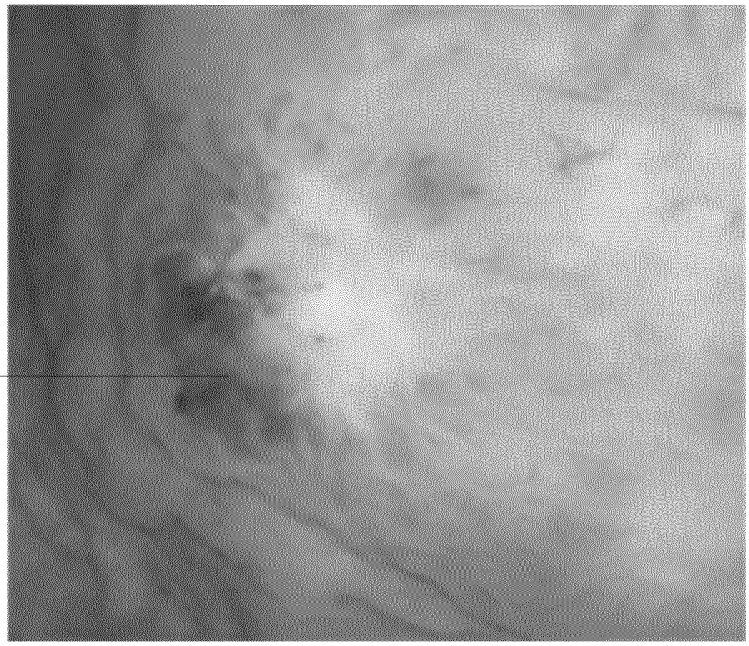

Fig. 2d

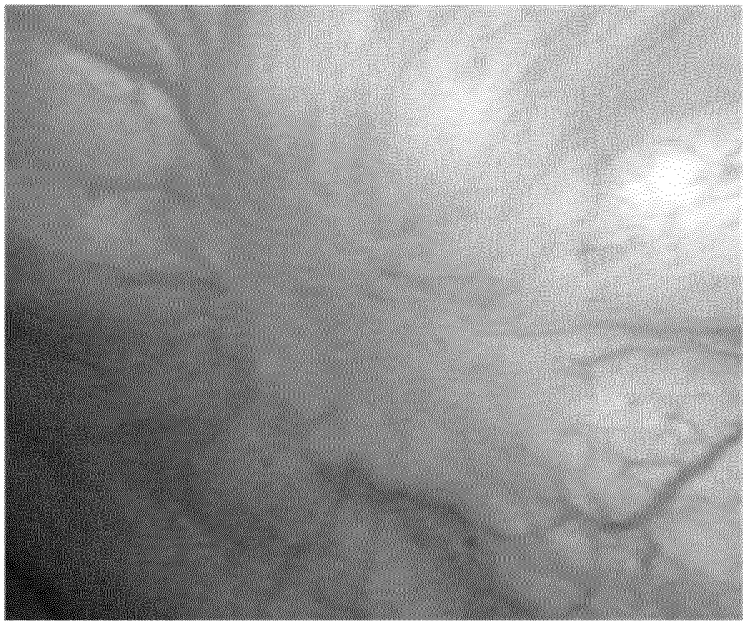

Fig. 2e

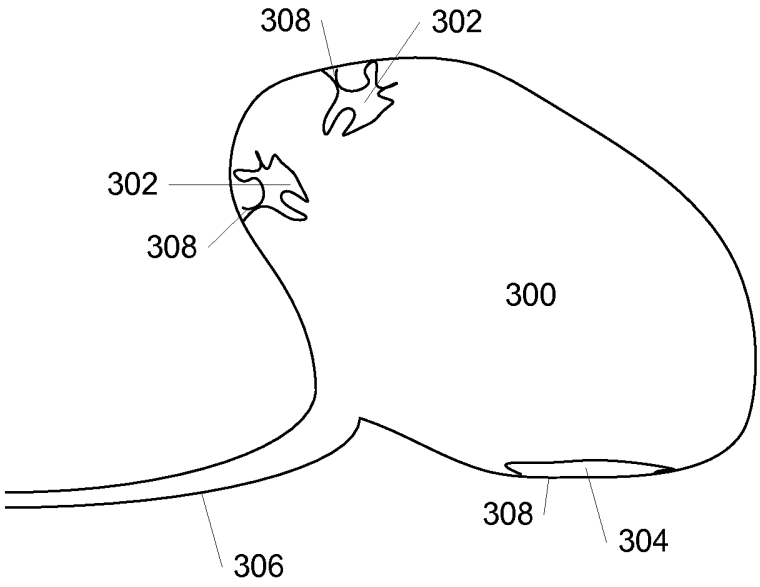
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Fig. 3

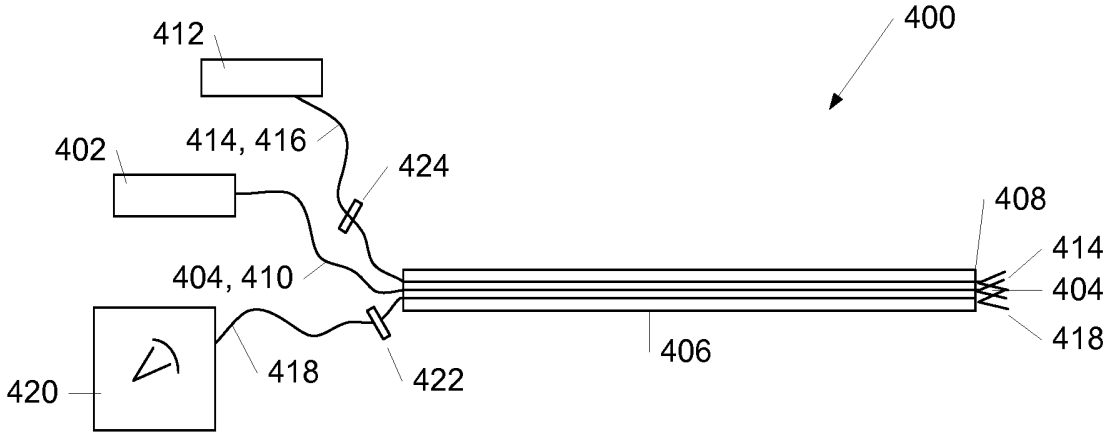
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Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/052521

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B18/24 A61B1/06
ADD. A61N5/06 A61B1/307

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61B A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/078160 A1 (MCMILLAN KATHLEEN [US]) 29 March 2012 (2012-03-29) paragraphs [0023] - [0028], [0041] - [0043], [0079], [0165], [0181], [0197], [0202], [0204], [0220], [0229] figures 28A,28B abstract	1-14
Y	WO 2013/092740 A1 (UNIV DENMARK TECH DTU [DK]; FREDERIKSBERG HOSPITAL [DK]) 27 June 2013 (2013-06-27) abstract page 3, lines 4-5 page 8, line 10 - page 9, line 35 page 11, line 18 - page 13, line 32 page 17, line 28 - page 18, line 24 page 23, lines 6-22 figure 11	1-14

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2016	19/04/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Grochol, Jana

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/052521

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2003/018324 A1 (DAVENPORT SCOTT [US] ET AL) 23 January 2003 (2003-01-23) abstract paragraphs [0013], [0031] claim 1 -----	1-14
A	US 2013/281845 A1 (LUIKEN GEORGE A [US]) 24 October 2013 (2013-10-24) abstract -----	1

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2016/052521

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 15-31
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/052521

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